Zinc intakes and plasma concentrations in men with osteoporosis: the Rancho Bernardo Study[1–3]

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ABSTRACT

Background: Low zinc intakes and reduced blood zinc concentrations have been reported to be associated with osteoporosis in women.

Objective: The objective was to examine the independent association between dietary zinc and plasma zinc and the association of each with bone mineral density (BMD) and 4-y bone loss in community-dwelling older men.

Design: Of the original Rancho Bernardo Study subjects, 396 men (age: 45–92 y) completed BMD measurements at baseline in 1988–1992 and 4 y later. Osteoporosis was defined as a BMD ≥ 2.5 SDs below the mean for young women (a *T*-score ≤ −2.5). At baseline, dietary intake data were collected by using a standard food-frequency questionnaire, and plasma zinc concentrations were measured by using inductively coupled plasma spectroscopy.

Results: The mean dietary zinc intake was 11.2 mg, and the mean plasma zinc concentration was 12.7 μmol/L. Plasma zinc was correlated with total zinc intake (diet plus supplements). Dietary zinc intake and plasma zinc concentrations were lower in men with osteoporosis at the hip and spine than in men without osteoporosis at those locations. BMDs for the hip, spine, and distal wrist were significantly lower in men in the lowest plasma zinc quartile (<11.3 μmol/L) than in men with higher plasma zinc concentrations. The association between plasma zinc and BMD was cross-sectional, longitudinal, and independent of age or body mass index. However, plasma zinc did not predict bone loss during the 4-y interval.

Conclusion: Dietary zinc intake and plasma zinc each have a positive association with BMD in men. *Am J Clin Nutr* 2004;80:715–21.

KEY WORDS Zinc intake, plasma zinc, osteoporosis, bone mineral density, men

INTRODUCTION

Osteoporosis is generally considered to be a disease of postmenopausal women; however, it is also an important public health issue in elderly men. About 30% of hip fractures occur in men, and 1 in 8 men older than 50 y will have an osteoporotic fracture (1). Until recently, the diagnosis of osteoporosis in men was based on fractures after minimal trauma. The introduction of bone density measurement methods, however, makes it possible to diagnose osteoporosis before fractures occur. The World Health Organization has defined osteoporosis as a bone mineral density (BMD) at the hip or spine that is ≥2.5 SDs below the mean value for young women, and osteopenia was defined as a BMD that is between 1 and 2.5 SDs below this value (2). These criteria may also be applicable in men (3, 4).

The development of osteoporosis in men is thought to be primarily related to aging, genetic factors, glucocorticoid use, hypogonadism, and assorted rare conditions (1, 4, 5). Some modifiable factors, such as excess alcohol consumption, smoking, physical inactivity, and deficiency or excess of some dietary components, are also associated with osteoporosis in men (1, 6).

The facts that the organic matrix in bone is mainly composed of protein and that most of the bone mineral content is calcium suggest that the important nutrients for bone health are protein and calcium (7). In addition to these nutrients, certain minerals and vitamins are probably required for the maintenance of healthy bone (7–10). Zinc is an essential trace mineral that is a component of >200 enzymes and is known to be necessary for normal collagen synthesis and mineralization of bone (11, 12). In animals, zinc deficiency has been associated with abnormalities in bone growth, bone formation, and mineralization (13). A significant positive correlation between human bone zinc content and bone strength suggests that zinc may play a role in bone health (14). Low zinc intake has been reported to be associated with low bone mass in women (15, 16). Furthermore, reduced serum or plasma zinc concentrations and increased urinary zinc excretion have also been reported in women with osteoporosis (17–20).

However, to our knowledge, little research on the association between zinc status and osteoporosis in men has been conducted. One epidemiologic study reported a higher fracture risk in men with low zinc intake than in men with higher zinc intake (21). The purpose of the present study was to examine the independent association between dietary zinc and plasma zinc concentration and the associations of each with BMD and 4-y bone loss in community-dwelling older men.

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SUBJECTS AND METHODS

Subjects

The Rancho Bernardo Study was established between 1972 and 1974 as a study of heart disease risk factors. All surviving men aged ≥45 y from the original Rancho Bernardo cohort who still resided in southern California were invited to participate in a study of osteoporosis. Between 1988 and 1992, 649 men completed standard questionnaires concerning smoking, alcohol use, physical activity, medication use, and disease history. Dietary intake data were collected. The height and weight of the participants were measured while they wore light clothing but no shoes, and body mass index (BMI; in kg/m^2) was calculated. BMD was measured, and plasma was obtained for the zinc assay. The study was approved by the Institutional Review Board of the University of California, San Diego. All participants provided written informed consent.

Between 1992 and 1996, 396 men (61%) returned for a follow-up visit, as close as possible to 4 y after their initial visit, for a second measurement of BMD; these measurements formed the basis of this report. The most common reasons for not returning for follow-up were death (≈30%), poor health, and having moved away.

Dietary intake

Dietary intake was assessed by using the Willett Diet Assessment questionnaire (22), which uses the food-composition database of the US Department of Agriculture. In men, the energy-adjusted, intraclass correlation for zinc intake between the 2 questionnaires collected 1 y apart was 0.64, and the energy-adjusted, deattenuated correlation from the food-frequency questionnaire for the average of two 1-wk dietary records was 0.71 (22).

Three subjects who reported extreme energy intakes (<500 or >4000 kcal/d) were excluded from further analysis. Information about the use of vitamin and mineral supplements that was obtained by a nurse, who examined pills brought to the clinic for that purpose, was used to calculate total micronutrient intakes.

Measurement of bone mineral density

During the baseline visit in 1988–1992, BMD was measured at the trochanter, intertrochanter, femoral neck, Ward's triangle, and lumbar spine by using dual-energy X-ray absorptiometry (Hologic QDR, model 1000; Hologic Inc, Waltham, MA) and at the midshaft radius and ultradistal wrist of the nondominant arm by using single-photon absorptiometry (Model SP2B; Lunar Corp, Madison, WI). Instruments were calibrated daily and had measurement precisions of ≤1% for the spine, ≤1.5% for the hip, 7.0% for the wrist, and 5.0% for the forearm. Total hip BMD was obtained by summing the bone mineral content values at the femoral neck, intertrochanter, and greater trochanter and dividing this value by the composite area of the 3 sites. Spine BMD was defined as the average BMD of lumbar vertebrae L1–L4. Forearm BMD was the mean of 4 lines at the midshaft of the radius. Wrist BMD was defined as the average of the 4 contiguous lines that yielded the lowest mean BMD. Osteoporosis for all axial sites was defined as a *T*-score ≤ −2.5, and osteopenia was defined as a *T*-score between −1 and −2.5 (2). Participants were seen as close as possible to 4 y after their initial visit during the second visit, which took place in 1992–1996. BMD was again measured at the total hip, trochanter, femoral neck, Ward's triangle, and lumbar spine, but the ultradistal wrist and midshaft radius were not measured at the second visit.

Measurement of plasma zinc concentrations

After the subjects had fasted overnight, blood samples were drawn into trace mineral–free plastic tubes each containing 2 drops of 2% sodium oxalate and were placed on ice. The blood was centrifuged within 2 h at 3000 × *g* for 10 min to obtain plasma. Plasma samples frozen at −70 °C were shipped on dry ice to the Mineral Analysis Laboratory at the Grand Forks Human Nutrition Research Center (Grand Forks, ND). Plasma zinc concentrations were measured by using an induction coupled plasma atomic emission spectrometer (Jarrell-Ash, Waltham, MA) (23). Analyses at the Grand Forks laboratory in which the results from the induction coupled plasma atomic emission spectrometer were compared with those from an atomic absorption spectrometer (Perkin-Elmer Corporation, Norwalk, CT) showed <5% variance, which was within the range of day-to-day variation.

Statistical analysis

SAS for personal computers (version 8.2; SAS Institute Inc, Cary, NC) was used for all statistical procedures. Because dietary zinc intake, total (diet plus supplements) zinc and calcium intakes, and plasma zinc concentrations showed skewed distributions, data were log transformed before the analysis. All *P* values for these variables were obtained on the basis of log-transformed data, but mean values were presented for untransformed data. Anthropometric variables, dietary intakes, and plasma zinc concentrations are shown as means ± SDs. Pearson's correlation coefficients were calculated to evaluate the associations of plasma zinc concentrations with age, BMI, and zinc intakes.

Mean age, BMI, nutrient intake, and plasma zinc concentration were compared between the men with osteoporosis, osteopenia, or normal BMD by using a generalized linear model. The proportions of men who smoked cigarettes, drank alcohol, or exercised regularly were compared between the 3 groups with the use of a chi-square test. Because osteoporosis status was significantly associated with age and BMI, differences in dietary intake and plasma zinc concentrations were compared after adjustment for age and BMI.

T-scores were not available for peripheral BMD measured by using single-photon absorptiometry. Therefore, plasma zinc concentrations were grouped into quartiles, and the age- and BMI-adjusted BMD values were compared betweem the 4 groups. Because the mean BMD was significantly lower for the lowest quartile than for the other 3 quartiles, the subjects were divided into 2 groups, ie, the lowest quartile of plasma zinc concentration (<11.3 μmol/L) and the other 3 quartiles combined. The differences in adjusted BMD between these 2 groups were tested by using a generalized linear model procedure. Three sets of outcome measures were compared in this analysis: BMD measured at the baseline (1988–1992), BMD measured at the follow-up visit (1992–1996), and percentage change in BMD between the 2 visits. To study whether some diseases or medications affected zinc concentrations, mean plasma zinc concentrations in participants who had or did not have these diseases or who did or did not take these medications were compared by using Student's *t* test.

TABLE 1
Baseline characteristics of the subjects

Characteristic	Value
Anthropometric variables (n = 396)	
Age (y)	69.9 ± 8.6[1]
Height (cm)	174.6 ± 6.5
Weight (kg)	80.4 ± 11.4
BMI (kg/m^2)	26.4 ± 3.3
Health behavior (n = 396) (%)	
Current smoker	8.6
Alcohol drinker[2]	90.9
Exercise ≥ 3 times/wk	78.5
Intakes (n = 375)	
Energy (kcal)	1812 ± 497
Protein (g)	73.9 ± 21.8
Animal protein (g)	50.6 ± 17.5
Thiamine (mg)	1.4 ± 0.5
Riboflavin (mg)	1.8 ± 0.7
Vitamin B-6 (mg)	2.1 ± 0.7
Folate (μg)	320 ± 115
Vitamin B-12 (μg)	7.0 ± 5.2
Iron (mg)	14.1 ± 6.0
Phosphorus (mg)	1203 ± 389
Dietary calcium (mg)	702 ± 347
Total calcium (mg)[3]	797 ± 446
Dietary zinc (mg)	11.2 ± 4.3
Supplemental zinc (mg)[4]	27.5 ± 25.8
Total zinc (mg)[5]	17.1 ± 17.3
Plasma zinc concentration (n = 396) (μmol/L)	12.7 ± 2.1

[1] $\bar{x}$ ± SD (all such values).
[2] At least one drink during the past year.
[3] Diet plus supplements (87 men were taking calcium supplements).
[4] For the 81 men who were taking zinc supplements.
[5] Diet plus supplements.

RESULTS

All 396 men were white. The baseline characteristics of the subjects are shown in **Table 1**. The mean age was 69.9 y (range: 45–92 y). The mean BMI was 26.4 (range: 17.0–42.1). Overall, 8.6% of the subjects were current smokers, 90.9% had drunk alcohol in the past year, and 78.5% reported that they exercised ≥3 times/wk. The reported mean energy intake was 1812 kcal, and the mean total calcium intake from the diet and supplements was 797 mg. The mean dietary zinc intake was 11.2 mg/d (range: 3.4–29.8 mg/d). Eighty-one men reported taking vitamin and mineral supplements that included zinc; the mean supplemental zinc intake was 27.5 mg/d in this subset. Total daily zinc intake from the diet and supplements averaged 17.1 mg, and the overall mean plasma zinc concentration was 12.7 μmol/L (range: 8.5–20.4 μmol/L).

As shown in **Table 2**, plasma zinc concentrations were not correlated with age, BMI, or dietary zinc intake. Plasma zinc was significantly correlated with total zinc intake (diet plus supplements).

Differences in anthropometric variables, health behaviors, selected nutrient intakes, and plasma zinc concentration by osteoporotic status assessed at the hip and spine are shown in **Tables 3** and **4**, respectively. Osteoporotic status at the hip was significantly associated with age, BMI, and smoking, and osteoporotic status at the spine was significantly associated with BMI. Age- and BMI-adjusted dietary zinc intakes, total calcium intakes, and plasma zinc concentrations differed significantly by osteoporotic

TABLE 2
Correlations of plasma zinc concentrations with age, BMI, and zinc intakes[1]

	Correlation coefficient	P
Age	−0.027	0.588
BMI	0.067	0.182
Dietary zinc intake	0.005	0.929
Total zinc intake[2]	0.114	0.027

[1] Pearson's correlation coefficients were calculated after plasma zinc concentrations, dietary zinc intake, and total zinc intake were log transformed.
[2] Data for diet plus supplements available for all 375 men.

status at the hip (Table 3) and the spine (Table 4). Age- and BMI-adjusted dietary and total zinc intakes, total calcium intakes, and plasma zinc concentrations were significantly lower in the men with osteoporosis at the spine than in men without osteoporosis at that location (Table 4).

Cross-sectional and longitudinal differences in age- and BMI-adjusted BMD between the participants in the lowest quartile of plasma zinc concentration (<11.3 μmol/L) and those in the other 3 quartiles combined are shown in **Table 5**. Compared with the men in quartiles 2–4, those in the lowest zinc quartile had baseline BMD values that were significantly lower at the hip, spine, and wrist but not at the midshaft radius. BMD values were measured 4 y later only at the hip and spine and were also significantly lower in the men in the lowest zinc quartile. However, 4-y changes in BMD did not differ significantly by baseline plasma zinc concentration.

Twelve potential confounding covariates for the association between zinc and BMD are shown in **Table 6**. Plasma zinc concentrations did not differ significantly by smoking status but were significantly lower in the men who reported no alcohol intake than in those who did report alcohol intake. The 81 men who took zinc supplements had significantly higher plasma zinc concentrations than did those who did not (13.5 compared with 12.5 μmol/L). Calcium supplements were not significantly associated with plasma zinc concentrations. Plasma zinc concentrations were significantly lower in the men who reported having ever been hospitalized or who had a history of osteoarthritis, rheumatoid arthritis, or a kidney stone than in those who did not. Stroke, diabetes, and the use of thiazides or steroids did not significantly affect plasma zinc concentrations. The low zinc concentrations in the men with osteoporosis were not explained by the factors that were associated with plasma zinc concentrations. After control for these factors, the low plasma zinc concentrations in the men with osteoporosis were not materially changed.

There was a strong collinearity of zinc intake with the intakes of other protein-related nutrients, such as riboflavin (r = 0.775), thiamine (r = 0.755), protein (r = 0.740), and iron (r = 0.726), and with the intakes of folate (r = 0.720) and energy (r = 0.641). After adjustment for energy intake, dietary zinc remained significantly (P < 0.001) associated with the intakes of riboflavin (r = 0.617), iron (r = 0.608), folate (r = 0.575), thiamine (r = 0.572), vitamin B-6 (r = 0.513), protein (r = 0.490), animal protein (r = 0.469), phosphorus (r = 0.373), and vitamin B-12 (r = 0.370).

TABLE 3
Cross-sectional characteristics depending on osteoporotic status at the hip[1]

Characteristic	Normal (n = 213)	Osteopenia (n = 153)	Osteoporosis (n = 30)	P
Anthropometric variables				
Age (y)	68.2 ± 0.6[c,2]	71.1 ± 0.7[b]	75.5 ± 1.5[a]	<0.001
BMI (kg/m^2)	27.4 ± 0.2[a]	25.5 ± 0.3[b]	24.6 ± 0.6[b]	<0.001
Health behavior (%)				
Current smoker	5.6	13.1	6.7	0.040
Alcohol drinker	91.1	91.5	86.7	0.696
Exercise ≥ 3 times/wk	77.9	81.7	66.7	0.177
Intakes[3]				
Energy (kcal)	1857 ± 36	1763 ± 43	1728 ± 93	0.187
Dietary zinc (mg)	11.7 ± 0.3[a]	10.5 ± 0.4[b]	10.8 ± 0.8[a,b]	0.019[4]
Total zinc (mg)[5]	18.0 ± 1.2	16.5 ± 1.5	14.0 ± 3.3	0.125[4]
Total calcium (mg)[6]	846 ± 32	743 ± 38	713 ± 84	0.040[4]
Plasma zinc concentration (μmol/L)[3]	12.9 ± 0.1[a]	12.6 ± 0.2[a,b]	11.8 ± 0.4[b]	0.022[4]

[1] Except for health behavior, a generalized linear model was used to compare the mean values for variables between the 3 groups. For health behavior, a chi-square test was used. Values with different superscript letters are significantly different, $P < 0.05$ (Tukey's test).
[2] $\bar{x}$ ± SEM (all such values).
[3] Adjusted for age and BMI.
[4] Analysis was based on log-transformed data.
[5] Diet plus supplements (81 men were taking zinc supplements).
[6] Diet plus supplements (87 men were taking calcium supplements).

DISCUSSION

In the present study, both self-reported zinc intake and measured plasma zinc concentrations were significantly lower in the men with osteoporosis at the hip or spine than in the men without osteoporosis. BMD values for all sites except the midshaft radius were significantly lower in the men in the lowest quartile of plasma zinc concentration (<11.3 μmol/L) than in the men with higher plasma zinc concentrations.

The overall mean dietary zinc intake in the subjects was 11.2 mg/d. This result is essentially identical to the 11.5-mg/d intake found in men aged ≥60 y who participated in the 1994–1996 Continuing Survey of Food Intakes by Individuals (24) and is similar to the 10.9-mg/d average dietary zinc intake found in elderly men aged ≥71 y who participated in the third National Health and Nutrition Examination Survey (NHANES III) in 1988–1994 (25).

The mean plasma zinc concentration for all subjects was 12.7 μmol/L, which is similar to the results from NHANES II in 1976–1980 (26) and an epidemiologic survey conducted in Rome (27). In the present study, plasma zinc was not correlated with age or BMI. Other researchers have reported no significant correlation of plasma or serum zinc with age (28–32) or BMI

TABLE 4
Cross-sectional characteristics depending on osteoporotic status at the spine[1]

Characteristic	Normal (n = 258)	Osteopenia (n = 98)	Osteoporosis (n = 40)	P
Anthropometric variables				
Age (y)	69.8 ± 0.5[2]	70.2 ± 0.9	69.9 ± 1.4	0.919
BMI (kg/m^2)	27.1 ± 0.2[b]	25.4 ± 0.3[a]	24.7 ± 0.5[a]	<0.001
Health behavior (%)				
Current smoker	7.4	8.2	17.5	0.102
Alcohol drinker	91.9	90.8	85.0	0.373
Exercise ≥ 3 times/wk	78.7	78.6	77.5	0.986
Intakes[3]				
Energy (kcal)	1855 ± 32	1736 ± 52	1713 ± 81	0.078
Dietary zinc (mg)	11.7 ± 0.3[a]	10.5 ± 0.5[a,b]	9.7 ± 0.7[b]	0.008[4]
Total zinc (mg)[5]	18.0 ± 1.1[a]	17.2 ± 1.8[a,b]	11.4 ± 2.8[b]	0.010[4]
Total calcium (mg)[6]	835 ± 29[a]	752 ± 47[a,b]	665 ± 72[b]	0.010[4]
Plasma zinc concentration (μmol/L)[3]	12.9 ± 0.1[a]	12.6 ± 0.2[a,b]	12.1 ± 0.3[b]	0.049[4]

[1] Except for health behavior, a generalized linear model was used to compare the mean values for variables between the 3 groups. For health behavior, a chi-square test was used. Values with different superscript letters are significantly different, $P < 0.05$ (Tukey's test).
[2] $\bar{x}$ ± SEM (all such values).
[3] Adjusted for age and BMI.
[4] Analysis was based on log-transformed data.
[5] Diet plus supplements (81 men were taking zinc supplements).
[6] Diet plus supplements (87 men were taking calcium supplements).

TABLE 5
Cross-sectional and longitudinal differences in bone mineral density (BMD) between subjects in the lowest quartile (Q) of plasma zinc concentration (11.3 μmol/L) and those in the other 3 quartiles combined[1]

	Baseline BMD[2]			Follow-up BMD[3]			Change in BMD[3]		
	Q1 (n = 100)	Q2–Q4 (n = 296)	P	Q1 (n = 100)	Q2–Q4 (n = 296)	P	Q1 (n = 100)	Q2–Q4 (n = 296)	P
	g/cm^2	g/cm^2		g/cm^2	g/cm^2		%	%	
Total hip	0.93 ± 0.01[4]	0.97 ± 0.01	0.004	0.92 ± 0.01	0.96 ± 0.01	0.010	−2.08 ± 0.48	−1.83 ± 0.27	0.645
Femoral neck	0.72 ± 0.01	0.76 ± 0.01	0.002	0.72 ± 0.01	0.75 ± 0.01	0.007	−1.15 ± 0.58	−1.46 ± 0.34	0.645
Ward's area	0.53 ± 0.01	0.59 ± 0.01	0.001	0.54 ± 0.02	0.58 ± 0.01	0.026	1.74 ± 1.48	−1.02 ± 0.85	0.107
Trochanter	0.69 ± 0.01	0.72 ± 0.01	0.007	0.68 ± 0.01	0.72 ± 0.01	0.018	−1.46 ± 0.55	−1.13 ± 0.32	0.602
Intertrochanter	1.09 ± 0.02	1.14 ± 0.01	0.004	1.07 ± 0.02	1.11 ± 0.01	0.011	−2.50 ± 0.54	−2.17 ± 0.31	0.597
Spine	1.02 ± 0.02	1.08 ± 0.01	0.013	1.03 ± 0.02	1.09 ± 0.01	0.012	0.32 ± 0.49	1.18 ± 0.28	0.126
Distal wrist	0.39 ± 0.01	0.41 ± 0.01	0.014	ND	ND		ND	ND	
Midshaft radius	0.78 ± 0.01	0.80 ± 0.01	0.255	ND	ND		ND	ND	

[1] A generalized linear model was used to compare age- and BMI-adjusted mean BMD values between the 2 groups. ND, not determined.
[2] Adjusted for age and BMI at the first visit (1988–1992).
[3] Adjusted for age and BMI at the second visit (1992–1996).
[4] $\bar{x}$ ± SEM (all such values).

(29), but contradictory results showing a negative association between blood zinc and age (26, 27, 32, 33) or BMI (34) have also been reported. Our results showing that plasma zinc concentrations did not differ significantly by age may reflect the fact that our study participants were healthy community-dwellers who had survived for 4 y from their initial visit and were therefore able to make a follow-up visit; thus, elderly subjects with low zinc concentrations may have been excluded. Similarly, Savarino et al (33) reported that serum zinc concentrations in most nonagenarians or centenarians were within the range found in the elderly subjects (60–90 y of age) and hypothesized that low zinc concentrations could be an early sign of disease rather than age.

TABLE 6
Effect of selected variables on plasma zinc concentrations

Variable	Answer	n	Plasma zinc[1]	P[2]
			μmol/L	
Health behavior				
Current smoking	No	362	12.8 ± 0.1	0.124
	Yes	34	12.2 ± 0.3	
Alcohol drinking (in past 12 mo)	No	36	11.9 ± 0.3	0.009
	Yes	360	12.8 ± 0.1	
Zinc supplementation	No	294	12.5 ± 0.1	<0.001
	Yes	81	13.5 ± 0.3	
Calcium supplementation	No	288	12.6 ± 0.1	0.275
	Yes	87	12.9 ± 0.2	
Disease				
Hospitalization	No	348	12.8 ± 0.1	0.020
	Yes	48	12.1 ± 0.3	
Osteoarthritis	No	317	12.8 ± 0.1	0.022
	Yes	79	12.2 ± 0.2	
Rheumatoid arthritis	No	383	12.8 ± 0.1	0.027
	Yes	13	11.5 ± 0.4	
Kidney stone	No	342	12.8 ± 0.1	0.027
	Yes	54	12.2 ± 0.3	
Stroke	No	376	12.7 ± 0.1	0.776
	Yes	20	12.6 ± 0.5	
Diabetes	No	362	12.7 ± 0.1	0.739
	Yes	34	12.8 ± 0.4	
Medication use				
Thiazides	No	372	12.7 ± 0.1	0.514
	Yes	24	13.1 ± 0.5	
Steroids	No	386	12.7 ± 0.1	0.141
	Yes	10	13.6 ± 0.7	

[1] $\bar{x}$ ± SEM.
[2] Student's t test was used after plasma zinc concentrations were log transformed.

In the present study, plasma zinc was correlated with total zinc intake, including intake from supplements, but not with dietary zinc intake alone. The absence of an association between dietary zinc intake and plasma zinc is concordant with the results of other studies (30, 35, 36). Dietary zinc may correlate poorly with plasma zinc because food-frequency questionnaires estimate annual intake whereas plasma zinc reflects recent intake. The bioavailability of zinc may also differ according to dietary sources and other components of the diet (37, 38). In addition, plasma or serum zinc, the most widely used indicator of zinc status, can be affected by physiologic factors, medications, and diseases (39, 40).

In the cohort in the present study, the osteoporotic men did not consume less energy than did the nonosteoporotic men, but the osteoporotic men were significantly thinner (Tables 3 and 4). Caloric intake is difficult to estimate from food-frequency questionnaires (41). This is the reason we adjusted our analyses of the association between osteoporosis and zinc for BMI instead of energy intake (41).

According to the results of the NHANES II study, 60% of dietary zinc is derived from meat products and milk (42). Except for folate, most of the nutrients that were correlated with zinc intake were from animal products (*see* Results). The strong collinearity between zinc intake and other protein-related nutrients precludes the designation of any single nutrient, including zinc, as causally associated with osteoporosis. We previously reported that animal protein (correlated with zinc) is positively associated with BMD among Rancho Bernardo study participants (43).

The results reported in the present study are concordant with those of studies showing an inverse correlation between zinc intake and bone loss in postmenopausal women (15), a significant cross-sectional correlation between forearm bone mass and zinc intake in premenopausal women (16), and an elevated fracture risk in men with low zinc intake (21). A few other reports

show low plasma zinc concentrations in osteoporosis. Kennedy et al (44) reported that the low plasma zinc concentrations observed in patients with rheumatoid arthritis are related to their degree of osteoporosis. Atik (45) found lower plasma zinc concentrations in 10 patients (sex not specified) with senile osteoporosis than in 12 patients without osteoporosis. Gur et al (17) reported that serum zinc concentrations were significantly lower in 70 postmenopausal osteoporotic women than in postmenopausal nonosteoporotic women. Lowe et al (18) reported that plasma zinc concentrations were significantly lower in 11 elderly osteoporotic women than in younger women.

Low blood zinc concentrations have been associated with inflammation, severe liver disease, malignant diseases, rheumatoid arthritis, and the use of steroids and diuretics (39, 44). In the present study, several medical factors, including hospitalization, osteoarthritis, rheumatoid arthritis, and kidney stones, were associated with significantly lower plasma zinc concentrations (Table 6), but these factors did not explain the observed association between zinc and osteoporosis.

Several groups of investigators reported higher urinary zinc (19, 20, 46–48), sometimes without differences in plasma zinc concentration (19, 46), in persons with osteoporosis than in those without osteoporosis. For example, Relea et al (19) showed that urinary zinc excretion, but not plasma zinc concentration, differed between postmenopausal women with or without osteoporosis. They also reported a negative correlation between total-body bone mineral content and urinary zinc excretion in the women with osteoporosis. However, the physiologic significance of urinary zinc excretion is unknown.

To our knowledge, the present study is the first study associating plasma zinc concentrations with BMD in elderly men. The association was cross-sectional and longitudinal but did not predict bone loss during the 4-y interval, possibly because of the relatively small bone loss during a relatively short, 4-y period. The study does not exclude a potential increase in BMD with increased dietary zinc intake in older men. Further studies are needed to evaluate a possible role for zinc deficiency in the etiology of osteoporosis in men. Clinical trials will be necessary to unravel the potential independent role of zinc in osteoporosis.

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